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| EXAMINER |
|---|
| PORTNER, VIRGINIA ALLEN |

| ART UNIT | PAPER NUMBER |
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| 1645 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

| Office Action Summary | Application No. 09/927,788 | Applicant(s) Mahan et al |
|---|---|---|
| | Examiner Portner | Art Unit 1645 |

-- *The MAILING DATE of this communication appears n the cover sheet with the corresp ndence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Jun 23, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-4, 7-9, 12, 13, 15, 18, 20, 22, 30, and 31* is/are pending in the application.

4a) Of the above, claim(s) *30 and 31* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 7-9, and 12* is/are rejected.

7) ☒ Claim(s) *13, 15, 18, 20, and 22* is/are objected to.

8) ☒ Claims *1-4, 7-9, 12, 13, 15, 18, 20, 22, 30, and 31* are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

**DETAILED ACTION**

Claims 30-31 stand withdrawn from consideration.

Claims 1-4, 7-9, 12-13, 15, 18, 20, 22 and 30-31 are pending.

Claims 1-4, 7-9, 12-13, 15, 18, 20, 22 are under consideration.

Claims 5-6, 10-11,14,16-17, 19, 21 and 23-29 have been canceled

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION**

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 23, 2003, has been entered.

***Allowable Subject Matter***

3. Claims 13, 15, 18, 20 and 22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Rejections Withdrawn***

4. Claim 3 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the amendment of claim 3 to be an independent claim and no longer to depend from claim 1.

***Rejections Maintained***

5. Claims 3-4 (amended) are rejected under 35 U.S.C. 102(e) as being anticipated by Curtiss, III et al (US Pat. 6,383,496), for reasons of record in paper number 14, and arguments set forth below in response to Applicant's traversal of the applied Curtiss, III et al reference.

***Response to Arguments***

6. The rejection of claims 3-4 under 35 U.S.C. 102(e) as being anticipated by Curtiss, III et al (US Pat. 6,383,496) is traversed on the grounds that:

a. the Curtiss patent US 6,383,496 does not disclose "the Dam activity is altered by a heterologous nucleotide sequence (independent claim 3)".

7. It is the position of the examiner that the instantly claimed invention of independent claim 3, does not require the alteration to be in the dam gene, but the attenuated live bacteria must only evidence a **different phenotypic activity** based upon altered DAM activity and the altered

activity is disclosed to produced through a mutation that is an insertion (a second heterologous nucleotide sequence, see col. 11, lines 21-35).

(Instant claim 3) The insertion of the second heterologous nucleotide sequence would be in the rpoS gene and/or in the aro gene, phoP gene or a combination of any of the additional genes disclosed at col. 11, lines 14-35 (amended instant claim 3), and the first heterologous nucleic acid would encode an antigen. Curtiss, III et al refers to the polynucleotide sequence that encodes an antigen as the second recombinant gene product; this gene product would be the same or equivalent product that Applicant refers to as the first heterologous nucleic acid that encodes an antigen (see Curtiss, III et al, col. 12, lines 34-67; col. 13, lines 1-54). The second heterologous nucleic acid may be considered to be the heterologous polynucleotide that is inserted into the coding sequence of the inactivated gene (ie. Aro gene, phoP gene, rpoS genes); or the second heterologous gene could be considered to be the complementary gene that is carried on a second plasmid (see col. 10, lines 22-26; col. 16, line 37;col. 18, line 57) and referred to as balanced lethal mutants (see col. 14, lines 19-41) . Heithoff et al (1999, page 969, col. 2, second half of first paragraph, reference of record) states that it is possible that PhoP (-) strains have different amounts of DAM activity.

Therefore, Curtiss, III et al, (US 6,383,496) discloses, and claims live attenuated strains of Salmonella bacteria that inherently evidence altered DAM activity and comprise first and second heterologous nucleotide sequences, specifically one being a coding heterologous nucleotide sequence for a heterologous antigen for a pathogen, specifically a virus, bacterium, protozoan or

fungus (see Curtiss III, et al, priority document '961, claims 19, 34-38), another heterologous nucleotide sequence that inactivates at least an aro gene, or phoP gene, by insertion (support in priority document '961, col. 8, lines 52, 58 and 60) that inherently alters DAM activity (as evidenced by Torreblanca et al (1996) or Heithoff et al (1999)), as well as the insertion of a recombinant rpoS+ nucleotide sequence into the live attenuated bacterium; the rpoS gene altering the activity and growth of the cell, thus altering the phenotype and activity of Dam .

(Instant claim 4) Curtiss, III teaches the utilization of a plurality of plasmids for the attainment of the live, attenuated, mutant strains of bacteria that comprise a mutation that alters Dam activity (relative to the wild type strain that is unaltered), expresses a heterologous antigen, and also comprises an rpoS+ recombinant gene that alters cell function and therefore alters Dam activity. Utilization of more than one plasmid to produce the live attenuated strains is disclosed, the plasmid encoded heterologous nucleotide sequences being the heterologous coding sequence for a heterologous antigen, and the coding sequence of the RpoS allele (see priority document '961, col. 7, line 58; col. 14, line 67 though col. 15, line 1; col. 11, lines 7-30; and '496, col. 38, Example 3, utilized two plasmids to produce the resultant attenuated live bacterium; col. 40, lines 11-24).

The rejection is maintained for reasons of record in paper number 14, and arguments set forth above. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or

of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

***New Grounds of Rejection***

8. Claims 1-2, 3-4, 7-9, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Collier et al (US Pat. 5,451,519)).

Collier et al disclose and claim a host cell composition directed to an attenuated live bacteria (E.coli dam mutant strain, see col. 24, claims 32-33), wherein the E.coli strain evidenced an altered DNA adenine methylase activity (increase mutations, decrease dam activity, see col. 20, lines 28-34 and Example 4, col. 20, lines 38-68) relative to the Dam activity of the wild-type, unaltered, pathogenic form of the live bacteria (the E.coli strain was a dam mutant, E.coli strain 3055 is (dam (-), see col. 19, line 30, which expresses B-galactosidase in response to DNA damage (see col. 19, lines 20-21, lines 64-65).

The compositions that comprised recombinant strains also comprised a first and second heterologous nucleotide sequence operatively inserted in the live attenuated (see col. 18, first and second plasmids, lines 1-9, and Example 2, col. 18, lines 38-47), which first heterologous sequence expresses a heterologous antigen plasmid encoded and expressed as S-adenosyl-L-methionine hydrolase or decarboxylase (see col. 13, lines 26-29 (T3 bacteriophage is a pathogenic virus for bacteria, and E.coli are known enteric pathogens), and col. 8, lines 30-33; col. 18, lines

41-43) and the second heterologous nucleic acid that encodes BamHII methyltransferase (see col. 18, lines 45-46).

The plasmid transformed recombinant host cell compositions was combined with an acceptable excipient (see col. 20, lines 54-56, and lines 64-68 to col. 21, lines 1-2; col. 20, lines 1-6). The reference anticipates the instantly claimed invention as now claimed.

9. Claims 1, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson et al (US Pat. 4,798,791).

Anderson et al disclose and claim an attenuated form of a live bacteria (see claims 20-22 and col. 8, claims 10-14) with a DNA adenine methylase activity altered (see col. 5, lines 9-16) relative to the Dam activity of the wild-type, unaltered, pathogenic form of the live bacteria (see claims 10-22, plasmid pGX2257 was obtained from E.coli strain GX3003 which contains a DNA adenine methylase (dam) mutation; see col. 5, lines 9-16), wherein the attenuated strain encodes and expresses a first heterologous protein antigen (see col. 8, claim 14 and 16); the attenuated live bacteria was combined with an acceptable excipient (see col. 6, lines 16-21; lines 52-67 and col. 7, lines 1-5; or cells in water, a type of excipient (see col. 7, line 21). The reference anticipates the instantly claimed invention.

10. Claims 1, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Berg et al (US Pat. 5,595,736).

Berg et al disclose an attenuated form of a live bacteria (see col. 23, dam(-) cell line E.coli K12 GM48) with a DNA adenine methylase activity altered (see dam (-), col. 23, line 30) relative to the Dam activity of the wild-type, unaltered, pathogenic form of the live bacteria , wherein the attenuated strain encodes and expresses a first heterologous protein antigen (see transformed with a plasmid that encodes a heterologous antigen, Figure 12, col. 23 lines 18-36) ; the attenuated live bacteria was combined with an acceptable excipient (see transformed cells were combined with a buffer pH 7.0, see col. 11, lines 60-62; col. 23, line 30 which refers back to col. 11, Example 1, section 1D, see figure 12). The reference anticipates the instantly claimed invention.

11. Claims 1, 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Shapiro et al (WO98/12206)

WO98/12206 disclose an attenuated live bacteria (cell transformed, page 12, paragraph 2; insertion mutant strain: see page 36, lines 1-2; also see over expression attenuation on page 37, paragraph 2; see page 487, claims 4, 9, 13, 17) with a DNA adenine methylase activity altered (see page 12, paragraph 4, "mutation in the enzyme"; see page 10, paragraphs 2-3; page 36, disrupted coding sequence) relative to the Dam activity of the wild-type, unaltered, pathogenic form of the live bacteria. Four different coding sequence for the methyltransferase genes were

disclosed from four different bacteria, including Helicobacter pylori and Brucella abortus, both enteric pathogens, as well as Rhizobium meliloti, and Agrobacterium tumefaciens.

The attenuated bacterial strains are taught to encodes and expresses a heterologous protein antigens (see heterologous antigen, page 7, paragraph 4, and page 8, paragraph 1; page 23, last paragraph line 7; see page 36 heterologous kanamycin/neomycin resistance marker; see page 36, bottom of first paragraph selection of functional copy of ccrM on a replicating plasmid; table on page 36 shows various levels of DNA adenine methylase enzymatic activity that are altered from the wild type strains LS2590 and LS2591, verses strains with disrupted ccrM coding sequence and supplemented with a plasmid, the level of Dam activity ( referred to as ccrM+) is reduced). The attenuated live bacteria are combined with an acceptable excipient glycerol (see page 37, section e., bottom of page, paragraph 5, first line). The reference anticipates the instantly claimed invention.

***Conclusion***

12. This is a non-final action.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hall (1990, abstract) is cited to show a dam mutant that expresses a heterologous antigen from a T4 bacteriophage. Tomes et al (US Pat. 5,773,697) is cited to show prokaryotic cells transformed with an expression vector that encodes DNA methylase (see claims 16, 13, 12, 10, 9, 4 and 1).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
August 21, 2003

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